REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. AGENCY USE ONLY *(Leave blank)*	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	20.Jan.04	THESIS

4. TITLE AND SUBTITLE
"GENDER DIFFERENCES IN RECOVERY TIMES FROM GENERAL ANESTHESIA USING SEVOFLURANE AND THE BISPECTRAL INDEX MONITOR"

5. FUNDING NUMBERS

6. AUTHOR(S)
CAPT ALGUIRE KATHERINE J

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
UNIVERSITY OF TEXAS HSC FT SAM HOUSTON

8. PERFORMING ORGANIZATION REPORT NUMBER
CI04-13

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)
THE DEPARTMENT OF THE AIR FORCE
AFIT/CIA, BLDG 125
2950 P STREET
WPAFB OH 45433

10. SPONSORING/MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION AVAILABILITY STATEMENT
Unlimited distribution
In Accordance With AFI 35-205/AFIT Sup 1

12b. DISTRIBUTION CODE

13. ABSTRACT *(Maximum 200 words)*

14. SUBJECT TERMS

15. NUMBER OF PAGES
66

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT

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GENDER DIFFERENCES IN RECOVERY TIMES FROM GENERAL ANESTHESIA USING SEVOFLURANE AND THE BISPECTRAL INDEX MONITOR

By

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A Cluster Research Study

submitted in partial fulfillment

of the requirements for the degree of

Master of Science in Nursing

The University of Texas Health Science Center at Houston

School of Nursing

December, 2003

Human Subjects Approval Letter

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NOTICE OF APPROVAL TO BEGIN RESEARCH December 30, 2002

HSC-SN-02-035 – "Gender Differences in Recovery Times from General Anesthesia Using Sevoflurane and the Bispectral Index Monitor (BIS)"
PI: Katherine J. Alguire, MSN; Keith Anderson

PROVISIONS: Unless otherwise noted, this approval relates to the research to be conducted under the above referenced title and/or to any associated materials considered at this meeting, e.g. study documents, informed consent, etc.

APPROVED: At a Convened Meeting

APPROVAL DATE: December 20, 2002 **EXPIRATION DATE:** November 30, 2003

CHAIRPERSON: Anne Dougherty, MD

Subject to any provisions noted above, you may now begin this research.

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CHAPTER I

Introduction

Optimization of patient care is one goal of anesthesia providers. With individualized care nurse anesthetists can achieve high degrees of patient satisfaction, reduce overall costs and improve patient outcomes. One concern for the anesthesia provider is the differing responses to pharmacological interventions between patients, especially between genders.

In the past, research in the area of gender differences was hindered due to Federal Food and Drug Administration (FDA) guidelines. Female subjects of childbearing years were excluded from participating in Phase I and early Phase II pharmacological clinical trials (Merkatz, Temple, Sobel, Feiden, & Kessler, 1993). In 1993, the FDA became aware of the need to include females in bioequivalence studies and released new guidelines regarding this (Chen et al., 2000). Following the release of these guidelines, research in the area of gender differences began to progress.

Statement of the Problem

This study investigated whether recovery times would differ between male and female subjects after they underwent general anesthesia using sevoflurane. To date, few studies have been done focusing primarily on gender differences in recovery time following general anesthesia. In a retrospective study, Gan et al. (1999) found that women emerged from general anesthesia significantly faster than men with the use of intravenous agents and nitrous oxide. Myles et al. (2001) found that women emerged faster than men from general anesthesia but had a slower rate of return to preoperative health status. Results of these studies indicated a need to investigate the possible influences of gender with regard to the administration of the various accepted general anesthetic agents.

Significance of the Problem

Inhaled anesthetics are widely used for the induction and maintenance of general anesthesia. They provide predictable intraoperative and recovery characteristics (Jellish, Lien, Fontenot, & Hall, 1996). There are numerous studies comparing recovery times following administration of various inhalational and intravenous agents. However, these studies do not include the effects of gender.

Discovery of significant gender differences in recovery times following general anesthesia using volatile anesthetics would be beneficial for individualized anesthetic management. The ability to determine which agent may be best suited for a particular subset of patients could lead to a faster recovery period and increased patient satisfaction. Improved prediction of recovery time might also allow for more efficient staff utilization and bed management in various recovery areas.

A study of this nature could also provide information that would be valuable for the preparation of deployed military units. Due to limitations already imposed upon operational facilities (e.g., supply, staff, space, etc.), knowledge of agents that would provide faster recovery for a specific population would be beneficial. The use of sevoflurane in this study would also be useful to the military because of restrictions regarding the type of inhaled anesthetics compatible with certain field anesthesia machines (885A and Narkomed M). Sevoflurane is one of the volatile anesthetic agents that is compatible for use in both the 885A and the Narkomed M.

Theoretical Framework

Consciousness is the key concept of this study (see Figure 1). Consciousness is a state of awareness. It implies an orientation to time, place, and person (Taber, 1985). The content of consciousness is a composite of memories and the comprehension of external reality; the emotional status and the individual's goals enter here. According

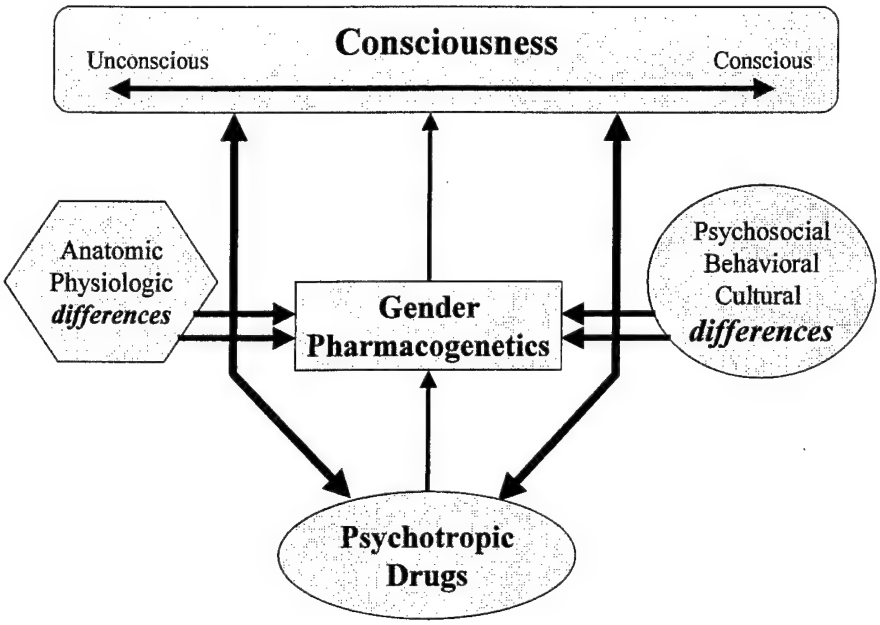

Figure 1. Influence of gender and other factors on recovery of consciousness from inhalational anesthetics. Consciousness is seen as a continuum. Psychotropic drug effects interact with this continuum through pharmacogenetic differences in humans. Differences arise when various sources (i.e. anatomic, physiologic, psychosocial , cultural, and behavioral) interact with the individual.

to Hobson (1997), there are concrete and abstract levels of consciousness. Human beings create an accurate representation of the world by processing sensory input from the external environment. Consciousness is the composite of the distinct yet interconnected concepts of perception, attention, memory, orientation, emotion, instinct, thought, and volition. For the purpose of this study, consciousness is a continuum, with full awareness and complete unconsciousness at opposite ends.

The basis for understanding how drugs elicit physiologic responses in an organism depends upon an understanding of the principles of pharmacokinetics and pharmacodynamics. Knowledge of these two concepts aids in understanding the theoretical framework for this study.

Pharmacokinetics deals with the absorption, distribution, biotransformation, and excretion of drugs across biologic membranes (Benet, 1996). In other words, the drug must enter the organism through various routes (e.g., orally, parenterally or by inhalation) and then move to target tissues or receptors. Once access is gained, the substance is circulated and distributed throughout the organism. During this process, the drug may be chemically altered or bound to an endogenous transporting substance (e.g., albumin). Finally, in an effort to re-attain homeostasis, the organism uses distinct physiologic and biochemical mechanisms to remove a drug (biotransformation and clearance).

Pharmacodynamics are defined by Ross (1996) as the study of the biochemical and physiological effects of drugs and their mechanisms of action as a means of gaining insight to how these drugs may be regulated by an organism. According to Ross (1996), theories have been generated about specific macromolecular components within an organism being the primary mechanism responsible for characteristic responses to drugs. These intracellular components, called receptors, bind with a chemical moiety (or drug) called a ligand, which in turn elicits a biochemical or physiologic response. This so-called "receptor-ligand theory" has been studied extensively and has given us valuable

insight to the mechanisms of how drugs interact within the human body.

Beyond the basic pharmacologic concepts of pharmacokinetics and pharmacodynamics, are those related specifically to the volatile inhaled anesthetic agents. Much controversy exists over the mechanism(s) and site(s) of action. According to Miller and Alifimoff (1998), neurophysiologists do not share the same opinions pertaining to the region or regions of the brain responsible for the maintenance of consciousness. Most of the research has focused on the reticular activating system in the central nervous system, but this is probably not the only site that regulates consciousness. Two theories prevail when considering action of the general anesthetics. The unitary theory of general anesthesia states that all general anesthetics exert their actions by a common mechanism. In contrast, the degenerate theory of anesthetic action postulates that different classes of anesthetics have different mechanisms of actions (Miller & Alifimoff, 1998). Because the mechanism of action remains unclear, gender may be an influence on differences in responses following administration of volatile anesthetics.

To date, there have been numerous studies dealing with male and female differences in the areas of nociception, antinociception, pharmacodynamics and pharmacokinetics. Both human and animal studies found that females had lower pain thresholds and tolerance when exposed to painful stimuli (Walker & Carmody, 1998). Bartok and Craft (1997) found female rats had greater antinociception than male rats when exposed to noxious stimuli in the presence of exogenous agents specific for a type of opioid receptor called the kappa receptor. In human studies, significant sex differences in analgesia were noted with the use of kappa opioids (Gear et al., 1996). Gender may also play a role in the metabolism of pharmacologic agents. In rats, this difference in metabolism has been attributed to the male levels of adrogenic (male sex hormone) hormones (Correia, 2001). Hooper and Qing (1990) found that young men had significantly increased elimination of mephobarbital as compared to young women and

elderly (>60 years old) men and women.

Purpose

The purpose of this study was to investigate gender differences in recovery times from general anesthesia using sevoflurane.

Definition of Terms

Body mass index. Conceptual definition: The subject's weight divided by his/her height^2 (BMI = Kg/m^2). A BMI less than 25 is normal and a BMI of more than 30 is obese (Longnecker, Tinker, and Morgan, 1998, p. 597-508). Operational definition: The same as the conceptual definition.

Gender. Conceptual definition: Being female or male; sex of an individual. Operational definition: Same as the conceptual definition.

Gender differences. Conceptual definition: The differences in experimental results due to gender. Operational definition: Differences in recovery time measured in minutes.

General anesthesia. Conceptual definition: Loss of sensation with loss of consciousness, when anesthetic drugs are administered (Gennaro et al., 1979, p. 334). Operational definition: BIS monitor reading of 40-60.

Light anesthesia. Conceptual definition: A less profound plane of general anesthesia, characterized by spontaneous respirations and normal vital signs (Miller and Alifimoff, 1998). Operational definition: BIS monitor reading 60-70.

Recovery time. Conceptual definition: The amount of time necessary for the patient to regain control of protective airway reflexes and appropriate levels of consciousness. Operational definition: Time from discontinuation of inhalation agent (Time = 0), patient will appropriately respond to verbal commands, open eyes and release hand grasp.

Research Question

Are there gender differences in recovery times from general anesthesia using sevoflurane and the Bispectral Index monitor?

Assumptions

The assumptions for this study are:

1. The subject would tolerate sevoflurane anesthesia.
2. The subject would have a normal recovery period.
3. BIS scores for men and women were the same (i.e., a BIS score of 75 was the same regardless of gender).

Limitations

The limitations for this study were:

1. This study used a convenience sample at one testing site.

Summary

Since 1993, research about gender differences has progressed. Gender differences have been found in the areas of nociception, antinociception, pharmacodynamics and pharmacokinetics (discussed in chapter two).

The ability to determine which anesthetic agent is best suited for a particular gender may provide for faster patient recovery, and increased patient satisfaction. Improved prediction of recovery time may allow for more efficient staff utilization and bed management. For the military, information about gender differences in recovery time could be beneficial to operational facilities during deployment. Establishing the importance of the use of sevoflurane in certain field anesthesia machines (e.g., Narkomed M and 885A) might benefit deployable medical assets.

No prior studies were found regarding gender differences associated with recovery time following general anesthesia using sevoflurane. The study investigated whether recovery time differed between male and female subjects after they underwent general anesthesia using sevoflurane.

CHAPTER II

Review of the Literature

A review of the pertinent literature was performed to synthesize key research and understanding in the areas of gender difference, sevoflurane (an anesthetic agent), bispectral analysis (or BIS monitoring) of general anesthesia, and the concept of awareness as it pertains to general anesthesia within the continuum of human consciousness.

Gender Differences

Two key studies elucidated potential differences between men and women with regard to recovery from general anesthesia. Gan et al. (1999) unexpectedly found a difference in recovery times between men and women (eye opening and response to verbal commands). Women emerged significantly faster than men when undergoing a propofol, alfentanil and nitrous oxide general anesthetic. This finding was secondary to the original hypothesis testing the efficacy of titrating hypnotic drugs using the Bispectral Index Monitor (BIS). The BIS is a device that non-invasively measures level of hypnosis. Additional research indicates gender-based differences in recovery time after anesthesia. Myles et al. (2001) found that women emerged from anesthesia faster than men but had slower returns to baseline health status and were more likely to have postoperative complications. Gan et al. (1999) found a gender difference of approximately 4 minutes and 3 minutes with regard to eye opening and responses to verbal commands, respectively. While these values were different, $p < .05$ the clinical significance of a 3-4 minute time difference remains questionable. A 10 minute difference in recovery time would be clinically significant in the areas of costs and staff utilization. More research is required to support these results. Additional research would provide insight into potential sources of difference associated with recovery from general anesthetic agents based on gender.

Pharmacokinetics. How the body interacts with drugs may be influenced by one's gender. The pharmacologic basis for these interactions has been expressed in both human and animal models. The following differences between males and females [liver metabolism, renal clearance, protein binding, the effects of sex hormones, and body composition (e.g. obesity)] will be addressed.

There is evidence suggesting that males and females differ with regard to the elimination of drugs. One important path of drug elimination involves the liver. Compelling evidence exists regarding sex differences in the activities of the enzymes involved in the metabolism of drugs and steroids in the liver. Additionally, hormones play an integral role in regulating these sex differences (Skett, 1988). Kato and Yamazoe (1992) found that most of the cytochrome P450 enzymes expressed in rat liver were sex-specific; these enzymes are regulated by various hormones and chemicals within the host. Hunt, Westerkam, and Stave (1992) studied the enzyme CYP3A, a prolific hepatic enzyme. They identified a 24% increase in hepatic CYP3A activity in human female hepatocytes (compared to males) during *in vitro* induction of Erythromycin N-demethylation (a form of hepatocyte activity). This suggests a direct gender-specific change in the protein, resulting in enhanced CYP3A activity in females.

The extent of protein binding, the volume of a drug's distribution throughout various body tissues, and its rate of elimination have also been studied by numerous investigators as potential sources of variability with regard to gender differences. Binding to plasma proteins (e.g., albumin or alpha$_1$-acid glycoprotein: AAG) is an important factor affecting the volume of distribution and elimination of drugs. Significantly lowered concentrations of AAG have been found in women taking oral contraceptives (OCP). In this study, the reduction of AAG in women taking OCP's was the main determinant of sex-related differences in lignocaine binding. Diazepam (a benzodiazepine used as an

adjuvant to anesthesia) also correlated, albeit weakly, to albumin and AAG concentration, and may be important when serum albumin levels are affected by aging or disease (Routledge, Stargel, Kitchell, Barchowsky, & Shand, 1981).

Greenblatt, Divoll, Harmatz, and Shader (1980) observed that sex was more important than age as a determinant of the clearance of the lipophilic medications; oxazezpam and temazepam. Diazepam, a highly lipophilic benzodiazepine, was found to have a higher volume of distribution and higher total clearance in young women versus young men (Ochs et al., 1981). Women tend to have lower ratios of lean body mass to adipose tissue (Kando, Yonkers, & Cole, 1995). It is reasonable to assume that more lipophilic drugs would have larger initial volumes of distribution and lower serum concentrations in women.

Obesity relates to body composition and body mass index and may play a role in the pharmacokinetic differences between men and women. Volume of distribution, when corrected for ideal body weight (IBW), was significantly greater in obese men, and tended to be greater in obese women when compared to their non-obese counterparts. Total clearance of acetaminophen increased with body weight regardless of age, and was higher in obese males than in female controls (Abernathy, Divoll, Greenblatt, & Ameer, 1982). A key study on midazolam kinetics in obese subjects found greater volumes of distribution, lowered serum albumin levels, prolonged elimination half-lives, and reduced total drug clearance (Greenblatt et al., 1984). In addition, females had larger volumes of distribution whether or not they were obese. This result is significant when considering a highly lipophilic drug like midazolam. It can also be related to another lipophillic agent, such as sevoflurane. The influence of obesity on drug disposition then, depends on the lipid solubility of the particular drug in question as well as its path of biotransformation or excretion (Greenblatt et al., 1984).

Hormones. Hormones may also be implicated in the pharmacokinetic differences between males and females. Evidence for sex differences exist in the activities of the enzymes involved in the metabolism of drugs and steroids in the liver. Hormones may be the primary regulators of these sex differences (Skett, 1988). What is not understood, however, is how these hormones induce changes in enzymatic activity. The effects of the sex steroids (estrogen, progesterone, testosterone, etc.) were studied by Gerdin and Rane (1992). *In vitro*, metabolism of ethylmorphine (a model substrate for inducing hepatic activity) was inhibited by sex hormones; this effect was not reproduced *in vivo*, however. Sex hormones also influence cellular function. For example, gonadal hormones may be involved in regulating natural killer cell activity; this phenomenon may be expressed differently between men and women (Yovel, Shakhar, & Ben-Eliyahu, 2001).

Sex hormones also play an important role in regulating cellular activity within the central nervous system (CNS). Gamma-aminobutyric acid (GABA) is the primary inhibitory neurotransmitter of the CNS, in mammals. The $GABA_A$ receptor is an integral membrane chloride channel that mediates most of the rapid inhibitory neurotransmission within the CNS, and has been linked with the effects of both intravenous and inhaled general anesthesia (Alifimoff & Miller, 1998). In one study, ovariectomized rats demonstrated a significant increase in the number of GABA binding sites when given exogenous estrogens and progesterone (Maggi & Perez, 1984). In a similar study, Lasaga, Duvilanski, Seilicovich, Afione, and Debeljuk (1988) found that estradiol increased GABA binding to sites within the hypothalamus in ovariectomized female rats, while testosterone decreased the number of similar GABA receptor sites in castrated male rats. GABA receptor production has been shown, in animal models, to increase in the presence of certain sex hormones (Lasaga et al., 1988). However, studies fail to link this important sexual dimorphism with consciousness and possible mechanisms of anesthesia, especially

in humans.

Sexually dimorphic pain perception and analgesia have also been investigated. Kepler et al. (1991) found significantly greater central morphine analgesia in male rats relative to females. Mogil et al. (1997) mapped a specific quantitative trait locus (QTL), or genetic variation, in a mouse model undergoing swim induced stress to test analgesic responses. Female mice were found to possess specific genetic traits for stress induced analgesia. These data provide evidence to support the concept of genetic and gender specific influences on pain and pain inhibition. In addition, Kavaliers, Colwell, and Choleris (1998) elicited sexually dimorphic opioid and non-opioid analgesic responses in deer mice exposed to biting flies. This was mediated through N-methyl-D-aspartate (NMDA) receptors within the CNS (non-opioid), and associates closely with anxiety, fearfulness, wariness and active defensive responses. Kavaliers et al. (1998) found that this form of analgesia was comparable between males and females but was not reversible in female mice, thus accentuating gender differences in antinociception.

Human studies questioning gender differences in analgesia or antinociception have also been performed. Using dental extraction as a model of moderately severe pain in humans, Gear et al. (1996) found that females had significantly greater analgesia than males associated with kappa-opioid agonists (i.e., nalbuphine) for post-operative pain. In a related clinical trial, Gear et al. (2000) found similar results with use of the kappa-opioid nalbuphine.

It is evident that anatomic, physiologic, and pharmacologic, gender differences exist. Specific mechanisms of sexual dimorphisms remain elusive making more research necessary to associate gender differences with anesthesia and recovery.

Sevoflurane

Inhalational anesthetics are the only agents capable of providing all aspects of

general anesthesia: muscle relaxation, unconsciousness and autonomic control. The older volatile inhalation agents were effective but had unpleasant side effects, including explosive (ability to explode) properties (Miller & Alifimoff, 1998). The discovery of less potent agents provided for increased patient safety. Today, the newer inhalational anesthetics are widely used for maintenance of general anesthesia because of their ease of elimination and predictable intraoperative and recovery characteristics (Jellish et al., 1996).The main basis for the speed of induction and recovery from general anesthesia is the solubility of the individual agents. The less soluble agents will approximate a F_A/F_I of 1 relatively quickly. In other words, the ratio of the fraction of alveolar gas (F_A) to the fraction of inspired gas (F_I) would be equal. This property allows for a quicker induction of general anesthesia. The agent will be sequestered into the lipid inhalational storage areas of the body at a slower rate. An anesthetic with a low blood:gas partition coefficient will have slower uptake, providing a more precise control of anesthetic effects (Smith, Nathanson, & White, 1995). The lower solubility will also allow for a more rapid elimination (Ibrahim et al., 2001).

Sevoflurane is a fluorinated methyl isopropyl ether inhalational anesthetic. This relatively new inhalational anesthetic agent displays many positive characteristics (such as low solubility and very non-irritating) with few side effects. The pharmacokinetic and pharmacodynamic properties of this agent make it advantageous for use in this study.

Sevoflurane has a low blood:gas partition coefficient of 0.686 and has a lower solubility compared to many other inhalational anesthetic agents (Strum & Eger, 1987). These properties are responsible for the faster induction of general anesthesia and the prompt recovery associated with this agent. The Phase I study of the characteristics and biotransformation of sevoflurane by Holaday and Smith (1981) supports this finding.

In numerous studies, sevoflurane provided for faster recovery from general

anesthesia compared with intravenous agents. Jellish et al. (1996) found significant difference in recovery time profiles between sevoflurane and propofol (8.8 minutes compared to 13 minutes respectively). Song, Joshi, and White (1998) found that sevoflurane and desflurane had shorter recovery times to awakening when compared to propofol (sevoflurane 5.2 +- 3.0 minutes, desflurane 4.7 +- 2.6 minutes compared to propofol at 8.3 +- 6.5 minutes). Sevoflurane was also significantly faster than propofol with regard to extubation time and time to orientation. In another study comparing recovery profiles between sevoflurane and propofol with fentanyl, sevoflurane provided faster emergence and recovery times (Peduto, Mezzetti, Properzi, & Giorgini, 2000).

Philip, Kallar, Bogetz, Scheeler, and Wetcher (1996) found significantly faster response times to eye opening and following commands with sevoflurane compared to isoflurane (7.0 +- 0.3 and 8 +- 0.3 compared to 9 +- 0.4 and 10 +- 0.4 minutes). A study by Ebert, Robinson, Uhrich, Mackenthun, and Pichotta (1998) confirmed that subjects on sevoflurane had a 3-4 minute quicker emergence time, response to following commands, and orientation, when compared to isoflurane. The faster emergence time from sevoflurane compared to isoflurane was attributed not only to the low solubility factor but also to the rapid decrease in blood concentration after discontinuation of the agent (Frink et al., 1992). However, sevoflurane may not have a faster emergence and recovery than the less soluble agents. Yasuda et al. (1991) found that the F_A/F_I of sevoflurane increased at a faster rate than isoflurane and halothane (moderately soluble agents) but not the highly insoluble agents desflurane and N_20. Desflurane is known to provide a faster recovery profile in the early recovery period than sevoflurane. Other characteristics of desflurane and sevoflurane were similar (Nathanson, Fredman, Smith, & White, 1995).

In addition to rapid recovery, sevoflurane possesses other favorable characteristics such as minimal respiratory and cardiovascular side effects. It is used during inhalation

inductions because of the decreased pungency and low incidence of respiratory irritability (Ibrahim et al., 2001). During the maintenance phase of a general anesthetic, cardiovascular stability was maintained while using sevoflurane (Nathanson, Fredman, Smith, & White, 1995). This agent also provides less cardiovascular depression after induction general anesthesia when compared to propofol (Smith, Ding, & White, 1992). Other side effects such as nausea and drowsiness were significantly decreased in patients with use of sevoflurane versus isoflurane (Philip et al., 1996). Only 36% of the sevoflurane group experienced nausea during recovery compared to 51% in the isoflurane group. Drowsiness was noted in only 15% of patients in sevoflurane group versus 26% of patients in the isoflurane group. In contrast, Frink et al. (1992) found that the incidence of postoperative nausea did not differ between sevoflurane and isoflurane.

The negative side effects of sevoflurane include the breakdown to fluoride ions and the production of compound A. This has been implicated as a mechanism of nephrotoxicity encountered with fluorinated hydrocarbons (like the inhaled anesthetics).

Serum fluoride levels are associated with the metabolism of sevoflurane. Smith, Ding, and White (1992) found serum fluoride levels were significantly higher following administration of sevoflurane compared to isoflurane and this level increased with exposure time. This finding correlated to the earlier finding that the degradation of sevoflurane resulted in higher serum fluoride concentrations than isoflurane, halothane and enflurane (Shiraishi, & Ikeda, 1990). Although the increase in serum fluoride levels could potentiate nephrotoxicity, no patients in either study presented with this complication.

Sevoflurane will also react with the carbon dioxide absorbents (soda lime and baralyme) in anesthesia machines. The product of this reaction will produce a haloalkene fluoromethyl-2, 2-difluoro-1-vinyl ether called compound A (Kharasch & Jubert, 1999).

The reaction is directly related to use of sevoflurane and fresh gas flow rates less than two liters. In rats, compound A can cause tubular necrosis leading to nephrotoxicity (Fang, Kandel, Laster, Ionescu, & Eger, 1996). It has been theorized that humans may be at risk for nephrotoxicity from compound A, (Kharasch & Jubert, 1999) but caution is advised when applying findings from animal models to humans.

Awareness and Bispectral Index (BIS)

Awareness is a state of perception and consciousness (Ouellette & Simpson, 1998). Awareness while under general anesthesia is a concern for all anesthesia care providers. Intraoperative awareness may present as an episode of recall. The patient may be able to relate specifics about the procedure or may display behavioral changes after the procedure. The highest frequency of recall occurs during the maintenance phase of an anesthetic.

In a closed claim analysis, 79 of the 4,183 (1.9%) claims were for awareness while undergoing a general anesthetic (Domino, Posner, Caplan, & Cheney, 1999). The reported incidence of awareness is approximately 0.2 to 0.4 percent in non-obstetric and non-cardiac surgical procedures (Domino et al., 1999). For cardiac, obstetric and trauma surgical procedures the incidence is higher. The women had an approximately threefold higher rate in the reported incidence of recall. Differences in physiologic responses to sedative-hypnotic medications (like propofol versus opioids and N_20) may account for females experiencing a higher incidence of intraoperative awareness (Domino et al., 1999).

The goal of anesthetic delivery is to prevent sensations related to pain and produce unconsciousness, thus inhibiting the risk that the patient will have recall of the surgical procedure (Halliburton, 1998). To provide for an adequate level of anesthesia, the anesthesia provider is continuously monitoring the depth of anesthesia. The BIS monitor

assists in the assessment of adequacy of the depth of sedation and hypnosis (Halliburton, 1998).

The goal of monitoring anesthetic depth is to provide for increased patient safety by decreasing the amount of anesthetic given to attain surgical anesthetic depth. There have been various theories regarding ways to monitor the depth of an anesthetic. Techniques include monitoring autonomic responses to noxious stimuli such as changes in heart rate and blood pressure (Halliburton, 1998). The presence of diaphoresis (diffuse sweating), pupillary dilation and lacrimation (tears, crying) are other autonomic responses assessed (Ouellette & Simpson, 1998). Movement in response to stimuli may be used to assess the responses of the somatic reflexes. Unfortunately, with the advent of neuromuscular blockade, this evaluation was hindered. Another indirect measurement used is minimum alveolar concentration monitoring of the inhalational anesthetic. The precise concentration of anesthetic agent that may be required to prevent intraoperative awareness is still unknown (Ghoneim & Block, 1997). However, minimum alveolar concentrations of all inhalational anesthetics at values of 0.8 to 1.0 percent are thought to prevent recall (Ghoneim & Block, 1997). However, these indirect measurements are not always reliable and may be inconsistent measurements of consciousness.

Direct measurements of consciousness provide a more reliable assessment of depth of anesthesia. The electroencephalogram (EEG) has been proposed as a monitor for anesthetic adequacy, but it requires qualified personnel to interpret readings and the equipment is bulky. In addition, the EEG results tend to vary with different anesthetic agents (Bard, 2001). The development of a user friendly and accurate monitor of hypnosis and sedation is essential.

The BIS monitor was used in this study to assess the level of hypnosis. It is derived from the EEG and integrates various EEG descriptors into a single variable (Johansen &

Sebel, 2000). The BIS decomposes the EEG signal into component sine waves and analyzes the phase relations between the component waves (Katoh, Suzuki, & Ikeda, 1998). The monitor analyzes and averages the signal, then reports a numerical value ranging from 0 to 100. A reading of 100 correlates to the awakened state and a reading of zero correlates to complete electrical inactivity consistent with comatose states (Johansen & Sebel, 2000). As the numerical value becomes smaller, the level of hypnosis becomes deeper. In 1996, the BIS monitor was approved for use as a clinical monitor to measure the effects of anesthetic agents on the central nervous system (Halliburton, 1998).

Numerous studies have investigated the reliability of the BIS monitor as a measure of sedation and hypnosis produced by anesthetic agents. Glass et al. (1997) found that the BIS monitor is a reliable measurement of the effects of hypnotic drugs. They found a strong relationship between BIS value and the state of consciousness in patients receiving propofol, midazolam, and isoflurane (Glass, 1997). Liu, Singh, and White (1997) confirmed that the BIS is valuable in monitoring amnesia during sedation or anesthesia induced with propofol. Song, Joshi, and White (1997) found the use of the BIS monitor decreased the maintenance dose of sevoflurane and desflurane and resulted in faster emergence times for patients in their study. Gan et al. (1997) demonstrated that hypnotic titration (using the BIS monitor) during anesthetic maintenance can speed emergence and recovery from anesthesia while reducing propofol doses. It is interesting to note that an unexpected finding from this study was that women emerged faster from general anesthesia than men (using propofol, alfentanil and nitrous oxide). They also found that at the same propofol concentration as men, women displayed a higher BIS number correlating to a more awake state (Gan et al., 1999).

The hypnotic component of sevoflurane has been shown to correlate well with BIS monitor values in various studies. Katoh et al. (1998) found that BIS values relate linearly

with sevoflurane concentration in all age groups. They also found that the BIS monitor provided better prediction of the depth of sedation than did end tidal concentration of sevoflurane (Katoh et al., 1998). When used during general anesthesia with sevoflurane, the BIS monitor may accurately predict various endpoints (loss and return of consciousness) (Olofsen & Dahan, 1999). Another advantage of using the BIS monitor for titration of sevoflurane is a reduction in the incidence of postoperative nausea and vomiting (Nelskyla, Yli-Hankala, Puro, & Korttila, 2001).

There are some finer points that need to be considered while using the BIS monitor for evaluation of depth of anesthesia. Artifact from other electrical equipment used in the operating room may interfere with actual BIS measurements. Thus, the value assessed is a trend rather than an absolute value. The hypnotic assessment is the only component measured by the BIS and does not correlate with the blood concentration of any one particular drug (Bard, 2001; Degoute, Macabeo, Dubreuil, Duclaux, & Banssillon, 2001). Opioid administration does not affect BIS levels (Johansen, & Sebel, 2000). Therefore, opioids can be utilized and allow for titration of sevoflurane. In the study by Badrinath, Avramov, Papaioannou, and Ivankovich (1999), the use of the BIS monitor decreased the dose of propofol required, but a higher dose of opioid was used without affecting BIS values. Sebel et al. (1997) found that there was good correlation between changes in BIS values and the probability of movement with propofol and isoflurane but not with the use of opioids. Some patients may display low EEG signals, resulting in what appear to be abnormally low BIS awake readings (Schnider, Luginbuhl, Peterson-Felix, & Mathis, 1997). In these patients, the BIS would be an unreliable indicator of hypnosis. Therefore, there is a need to obtain a baseline BIS value before the induction of anesthesia.

Summary

There was an apparent lack of research exploring the differences between males and

females recovering from general anesthesia. From a pharmacologic perspective, gender differences in drug kinetics and dynamics clearly existed but many of the phenomena exhibited in clinical research are still poorly understood.

Sevoflurane is one of the least potent (lowest solubility) inhalation anesthetics available for use today. This agent has properties that will provide a safe and relatively predictable anesthetic delivery. The rapid uptake, elimination, and the low incidence of side effects of this potent inhalation agent made it suitable for use in this study.

The BIS monitor is a good indicator of anesthetic depth when using a hypnotic agent. The usefulness of monitoring with the BIS is dependent upon the anesthetic technique used (Sebel et al., 1997). Studies have provided information that display evidence that the level of sedation/hypnosis provided by sevoflurane correlates with BIS values. The use of the BIS monitor in this investigation enabled a more precise control over the depth of anesthesia produced by sevoflurane.

CHAPTER III

Methodology

The purpose of this study was to investigate whether a difference exists between males and females in recovery time following general anesthesia using sevoflurane. A quasi-experimental study design was used. This section provides a description of the population, sample and setting. The instrumentation and data collection procedures will be introduced. Protection of human subjects, the study design and the data analysis will also be discussed.

Population, Sample, and Setting

The population for this study consisted of adult (male and female) subjects presenting to a medical treatment facility for elective surgery. The setting was the operating rooms of a large medical center on the West coast. A convenience sample was obtained.

The initial sample included 30 male and 30 female patients. Because of attrition (length of surgery, opioid dose, and low BIS values) 22 males and 27 females completed the study. Subjects were healthy overall, as determined by their physical status (American Society of Anesthesiologists class I or II). Subjects aged 18 to 55 years were eligible for enrollment. The actual surgical time was limited to a length of greater than or equal to 45 minutes but less than or equal to 180 minutes.

Exclusion criteria for this study included several factors. Subjects with a BMI greater than 30% were not enrolled in this study secondary to increased risks of surgical complications associated with obesity and the possibility of confounding variability related to the redistribution of medications. Subjects who had previously undergone general anesthesia in the last two weeks and pregnant females were also excluded from the study. Persons with a history of cardiac, pulmonary, renal, hepatic or neurological diseases were excluded. Subjects with known severe psychiatric diseases, any previous history of substance abuse or chemical dependency were also excluded.

A power analysis using data obtained by Gan et al. (1999) was done. Gan et al. (1999) found a statistically significant difference of approximately 3-4 minutes in recovery times between male and female subjects using a balanced anesthetic technique consisting of propofol, alfentanil, and nitrous oxide. This finding was statistically significant but some would not consider these results clinically significant. In this study, we sought to detect a clinically and statistically significant difference in recovery time of approximately 10-minutes between groups (a "large" effect size). With a population size of 60, and alpha of 0.05 we derived a power of .80.

The subjects were identified for enrollment in the study on the day of surgery during the preoperative interview and assessment.

Instrumentation

A data collection tool was created to obtain all demographic data pertinent to the study. Additionally, this tool was used to collect intraoperative data. Other instruments used for supplemental information were the BIS monitor and an end tidal anesthetic gas monitor.

Data collection tool. The data collection tool contained all pertinent information for the study (see Appendix A). The tool, created by the authors of this study, had not previously been used. It contained demographic data such as - gender, age, height, and weight – collected from each subject during the preoperative assessment. The anesthesia provider determined the ASA physical status classification for each subject based on the preoperative interview and assessment. Body Mass Index (BMI) for each subject was estimated using the calculation, BMI = weight in kg / (height in meters)^2. Time was recorded for each point of recovery. Time zero was the time that the sevoflurane vaporizer was turned off. The vaporizer was turned off following completion of dressing application. The other two recovery points were the time at which the subjects first opened their eyes and time at which the subjects could perform a hand grip-release to

verbal command. Hand grip-release to verbal command was used because hand grip alone could have been a reflexive response rather than a sign of higher cortical functioning. Gan et al. (1997), Fredman et al. (1995), and Phillip et al. (1996) found eye opening and response to verbal command correlated well as end points for recovery from intravenous based anesthesia and sevoflurane based anesthesia respectively. The BIS scores, end tidal gas concentration of sevoflurane, and total dose of all adjunctive medication were recorded for each subject. The types and lengths of procedures were documented. The information on the data collection tool was obtained and recorded by the anesthesia provider.

BIS monitor. The BIS monitor was used on all subjects. The BIS value provides a numerical value that ranges from 0 to 100. The awake state of consciousness correlates to a BIS score of 100. A score of 0 indicates no electrical activity consistent with comatose state (Johansen, 2000). A BIS score less than 60 correlates with unconsciousness (Aspect Medical Systems, 2000). For the purpose of this study, a BIS score between 40-60 was considered to be consistent with hypnotic levels necessary for surgical anesthesia. The subjects in this study were maintained at a BIS level of 40-60 until the sevoflurane vaporizer was turned off.

The reliability and validity of the BIS monitor has been demonstrated in numerous studies. Glass et al. (1997) found that the BIS score correlated well with level of responsiveness, loss of consciousness and recall in a multiple center, randomized study of 72 subjects, receiving propofol, isoflurane, and midazolam. They found the prediction probability of the BIS values obtained were from 0.885 to 0.976, indicating a high predictability in correctly indicating loss of consciousness (Glass et al., 1997). Liu, Singh, and White (1997) found that the BIS score correlated with the depth of sedation of ten male patients receiving propofol during regional anesthesia. In a randomized study of 69 patients, BIS values were found to correlate with the level of sedation, and were

related linearly with concentration of sevoflurane (Katoh et al., 1998). In a multiple center study of 302 randomly assigned patients, Gan et al. (1997) found the BIS was a safe and efficacious measure of patient responses to propofol-alfentanil and nitrous anesthesia.

The BIS scores and vital signs were recorded simultaneously throughout each case. The scores obtained were averaged and recorded on the data collection tool. The BIS score was also recorded at each endpoint of recovery.

The medical equipment and repair center (MERC) office at this institution was responsible for the yearly calibration of the BIS monitor.

Procedure for Data Collection

Institutional Review Board (IRB) approval from the institution and university for protection of human subjects was obtained. After a thorough explanation of the study, informed consent was obtained from each subject by a study investigator. The subjects were evaluated for inclusion in the research study by the investigators. Data collection began preoperatively and continued until all endpoints of recovery had been met. Routine monitoring per protocol for every subject was done. This included: EKG, pulse oximetry, non-invasive blood pressure monitor, peripheral nerve stimulator, end tidal carbon dioxide monitor, and temperature monitor.

Preoperatively all demographic data were collected. Subjects were re-evaluated for inclusion and exclusion criteria. In the preoperative holding area, baseline vital signs and BIS values were recorded. Subjects with low preoperative BIS values (below 90) were excluded from the study. Each subject received midazolam .02 - .03 mg/kg intravenously. Subjects were transferred to the operating room before the induction of general anesthesia.

Induction of general anesthesia was accomplished with propofol and fentanyl. Propofol 2 mg/kg IV, the standard induction dose was used. Each subject also received

the potent opioid, fentanyl 2 mcq/kg IV. After establishing ventilation, if neuromuscular blockade was required, vecuronium 0.1 mg/kg IV was given. If rapid sequence induction was required, succinylcholine 1.0 mg/kg IV was given instead of vecuronium. The sevoflurane vaporizer was turned on and titrated to maintain anesthetic depth (per continuous BIS and end tidal agent monitors as well as vital signs). Fresh gas flow was ten liters during the induction phase. Cricoid pressure was established as necessary for subject safety.

General anesthesia was maintained with the volatile anesthetic sevoflurane and titrated to maintain anesthetic depth. Fresh gas flow during the maintenance phase was no less than two liters. If subjects required additional neuromuscular blockade, vecuronium .05 mcg/kg was given. For analgesia, fentanyl 0.5 to 3mcg/kg was given as needed. Subjects that required a total dose of fentanyl greater than 3 mcg/kg/hr, in addition to their induction dose, were dropped from the study because of the likelihood of this medication interfering with recovery time. Total doses of all anesthetic adjuvants were calculated and recorded for each subject.

Emergence from general anesthesia began after completion of surgical dressing application. The volatile anesthetic agent, sevoflurane, was turned off at this time. Fresh gas flows were increased to at least ten liters. When the sevoflurane vaporizer was turned to the "off" position, this time point was recorded as time zero for the data collection of recovery time. Neuromuscular blockade was reversed with neostigmine 0.05 mg/kg and glycopyrolate 0.01 mg/kg if indicated.

Recovery data was recorded in one-minute time intervals and for safety and consistency purposes was collected by two individuals. One investigator monitored time with a standard stopwatch (measuring in minutes and seconds). The other investigator monitored the subject and observed for the two endpoints (eye opening and hand grip/release). Measurement of recovery time began when the sevoflurane was turned off

and ended when subjects opened their eyes to verbal and tactile stimulation, and grasped/released the investigator's hand upon verbal command.

Protection of Human Subjects

The research investigators ensured the protection of human subjects. IRB approval from the institution and the university was obtained. Informed consent from each subject was obtained prior to inclusion in study.

Each subject was evaluated for inclusion and exclusion criteria. If the subject met criteria for inclusion in the study, the investigators gave a thorough explanation of the purpose of the study, the risks and benefits associated with participation in the study, and why the study was of importance to the medical community and to the subject. Enrollees were informed of their right to refuse to participate and to request to be removed from the study at any time. Subjects were then given an opportunity to ask questions. The subjects were ensured that anonymity and privacy would be maintained at all times.

Subjects were assigned a random number. This number was used for any results reported; the names of subjects were not used. Results of the study were available for each subject upon his/her request. If subjects were agreeable to inclusion in the research study, the appropriate consent forms were then completed and legal signatures obtained. A third party, not involved in the research study, witnessed the subject's signature.

Study Design

This study used a quasi-experimental design and consisted of two groups, males and females. The participants and investigators in this study were not blinded to any component of the investigation; each group received the same treatment and the anesthesia providers knew who the study participants were.

Potential threats to the internal validity of the study existed. These threats were thought to interfere with the effect of the independent variable (gender) on the dependent variable (recovery time). Confounding variables such as high doses of fentanyl, BMI,

length of surgery, and age of patient may have affected the outcome of the study but were accounted for using ANCOVA (see Findings, page 29). In addition, it is possible that the subject could have withheld pertinent information regarding medical history or he/she may have had an undiagnosed medical problem that could have emerged during the investigation. Attrition from the study and experimenter bias were also considered potential threats to the internal validity.

Potential threats to the external validity of this investigation existed. A selection bias could be inferred because of the non-randomized convenience sample technique employed. The sample (relatively young, healthy, military population) might not have been representative of the overall population; therefore generalizing results could be difficult. There could be experimenter effects; the investigators were not blinded to the subjects or treatments. The anesthesia provider was also the data collector therefore the responses of the subject were dependent on the providers' observations and judgments. Each data collector was trained on data collection techniques. The additional investigator measuring time (with the stopwatch) helped to offset the threat of experimenter bias. Ensuring adequate training of the anesthesia providers in data collection and documentation helped to control measurement effects.

Data Analysis

The data collected to answer the research question of whether gender differences (males versus females) exist in recovery times (measured in minutes) following general anesthesia using sevoflurane was analyzed using ANCOVA. The covariates that were controlled for were: opioid dose, BMI, length of surgery and age of the subjects. The assumptions for using ANCOVA (i.e, normality, homogeneity of variance and multicollinearity) were checked before performing the analysis.

Summary

In conclusion, this research study was a descriptive, non-randomized quasi-

experimental study. A convenience sampling technique was used. The sample was drawn from subjects presenting for elective surgical procedures at a West coast medical center. The subjects were exposed to the same medications and agents used for the induction, maintenance, and emergence of general anesthesia. Non-blinded anesthesia providers obtained data. Each subject gave informed consent. Confidentiality was maintained at all times. The results of the data collected were analyzed using ANCOVA.

CHAPTER IV

Analysis of Data

Following IRB approval and informed consent a convenience sample of 60 subjects was enrolled (30 men and 30 females) but only 22 men and 27 female subjects completed the study. Attrition was due to not meeting surgical time requirements (5 men and 2 females), total opioid dose/amount (1 male), and low BIS values (2 men and 1 female).

Description of Sample

Demographic data for both groups are shown in Table 1. Subjects from both groups were between the ages of 18 and 55 years of age. The average age for male subjects was 31 and for females 35. Males were to be taller and heavier than the female subjects. The BMI for both groups was approximately equal at 25%. A comparison of the types and frequencies of elective surgical procedures are displayed in Figure 2. The majority of subjects, in both groups, underwent general surgical procedures.

Findings

To determine if gender affected wake up times from general anesthesia using sevoflurane as measured by the BIS monitor, an analysis of covariance (ANCOVA) was performed. An alpha level of .05 was used for all analyses. The difference in wake up times was not statistically significant, $F(1, 43) = 0.292$, $p = .592$. On average, our sample of 22 males took 5.18 minutes to wake-up relative to our sample of 27 females who took 4.53 minutes (see Table 2). The covariates used in our analysis were not significantly related to wake-up time, $p > .05$ (see Table 3). The assumptions for multicollinearity, normality, and equal variance were met.

It was interesting to note that on average, men took numerically longer to wake-up than women. Another finding was that propofol dose and fentanyl induction dose

Table 1

Demographic Data

	Range		Arithmetic Mean	
	Male (n=22)	Female (n=27)	Male (n=22)	Female (n=27)
Height (in)	66-76	59-71	70.55	65.04
Weight (kg)	68-107	47.7-90	83.64	67.33
Age (years)	18-45	19-55	31.00	35.00
BMI (kg/m^2)	19.8-30	16.98-30	25.46	24.67

Table 2

Wake-up Time (in minutes) in Each group

Gender	Mean	Standard Deviation	N
Male	5.17	3.02	22
Female	4.53	2.33	27

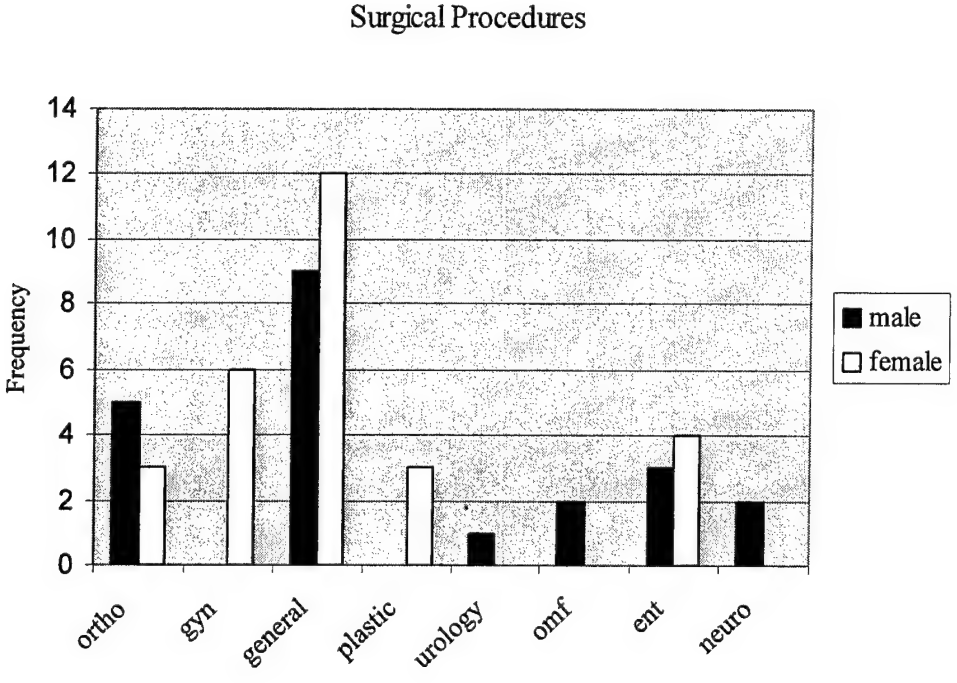

Figure 2. Frequency of each surgical procedure by group.

Table 3

Statistical Data for the Covariates

Parameter	Arithmetic Mean		F	Significance
	Males	Females		(p-value)
BMI (kg/m^2)	25.46	24.67	0.64	0.42
Age (years)	31.00	35.00	0.90	0.34
Surgical Length (minutes)	103.64	107.41	1.49	0.22
Total Fentanyl Dose (mcg)	312.27	287.78	1.99	0.16

were statistically different between groups, $p < .05$ (see Table 4); higher doses of the drugs were administered to men (dosing by kilogram weight). Table 5 displays the frequency of adjunctive medication given to both groups based on provider preference. Not all of the medication doses (mg) were statistically higher in men. The frequency of lidocaine administration between groups was found to be statistically different between groups using the Pearson Chi-Square test, $p = 0.006$. Men were given lidocaine more frequently than women based on provider preference.

BIS monitor values and end tidal sevoflurane readings were recorded every five minutes and at data collection end points. The BIS and end tidal sevoflurane values for male and female subjects were relatively the same at all data collection points. Preoperative BIS value average for both groups was 97. BIS value averages at time zero for the female group was 57 and for the male group was 59. The BIS values at eye

Table 4

Differences in Propofol and Fentanyl Dosing Between Groups

Medication	Gender	Mean	Standard Deviation	t-value	p-value
Propofol (mg)	Males (n=22)	169.55	22.57		
	Females (n=27)	132.04	23.75	-5.62	0.000001*
Fentanyl (mcg)	Males (n=22)	168.86	23.19		
	Females (n=27)	135.56	23.91	-4.91	0.000011*
Succinylcholine (mg)	Males (n=22)	57.73	52.05		
	Females (n=27)	32.12	43.22	1.86	0.068845
Vecuronium (mg)	Males (n=22)	8.30	4.83		
	Females (n=27)	5.72	4.05	-0.45	0.65358

Note. * = statistical significant $p < .05$.

opening and hand grasp for the female group was 86 and 88 respectively. The male group BIS value at the same end points was slightly higher than the female group, 90 for eye opening and 91 for hand grasp. End tidal sevoflurane values at time zero were the same for both groups at 0.8. End tidal sevoflurane values for both end points were .2 in both groups. Figures 3 and 4 display the average BIS and end tidal sevoflurane values for both groups.

Table 5

Adjunctive Medications Given

Adjunctive Medication Received	Female (n)	Male (n)	Pearson Chi-square Value	Significance (2-sided)
Lidocaine	9	16	7.53	0.006*
Antibiotic	15	16	1.54	0.21
Reversal Agents	20	11	3.02	0.08
Gastric Medication	22	15	1.16	0.28

Note. * = statistically significant $p < .05$.

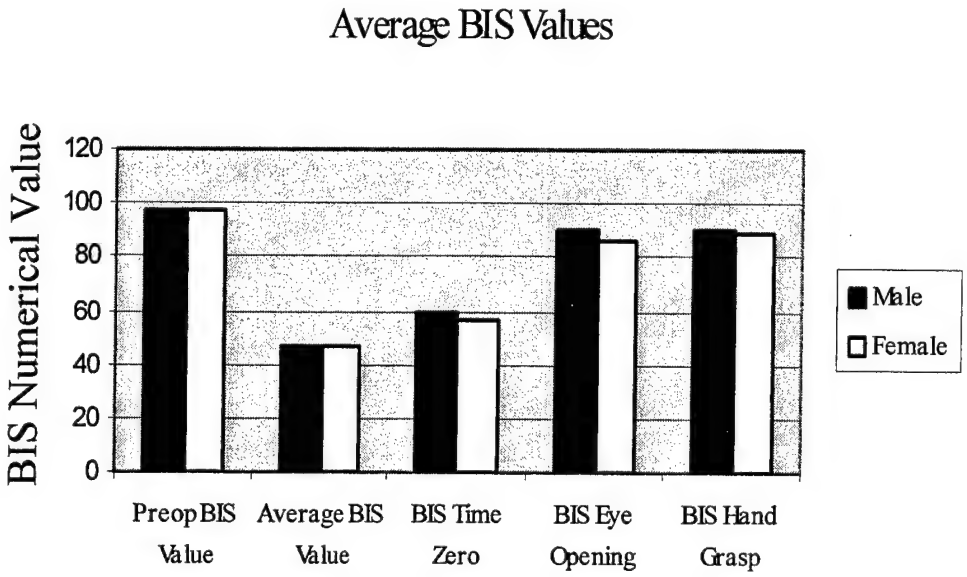

Figure 3. BIS values between groups.

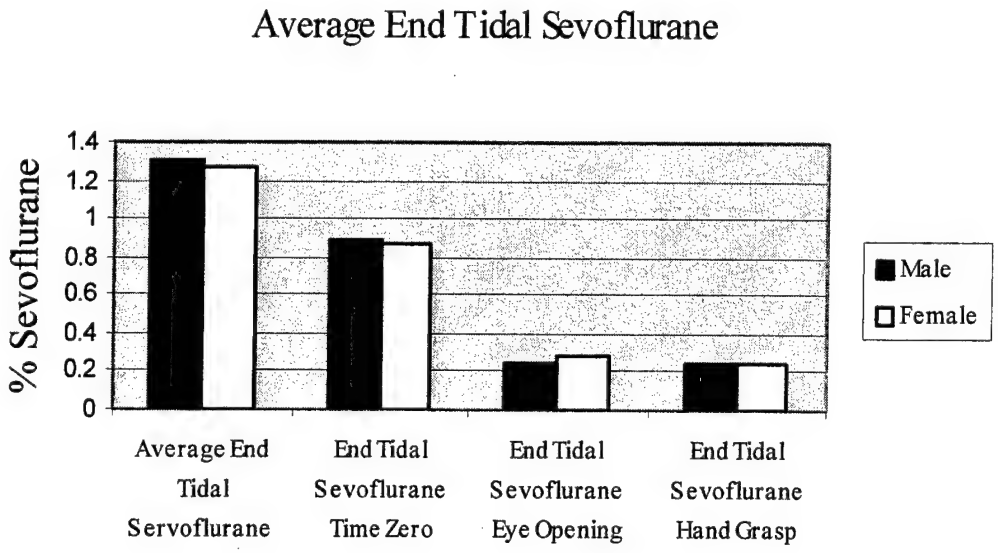

Figure 4. End tidal sevoflurane values between groups.

CHAPTER V

Discussion, Conclusions, Implications, and Recommendations

The purpose of this study was to investigate whether a difference exists between males and females in recovery time following a general anesthetic using sevoflurane. Discussion of the results from this study follow, including an interpretation of the findings in relation to our theoretical framework and an evaluation of the strengths and weaknesses of the research. We will conclude with clinical implications of this research as well as suggestions for further research.

Discussion

Few studies, to date, have specifically investigated the role that gender may have on recovery from general anesthesia. It has been suggested that there may, in fact, be gender differences in recovery. The implications of this finding may impact the methods or drugs employed when general anesthesia is conducted. Our research question was, whether there are gender differences in recovery times using sevoflurane? As previously discussed in the results section, we found that while there was not a statistically significant difference in the time it took for males or females to emerge from the anesthetic, females in our study recovered up to 1 minute faster than males. These findings would seem to support our theoretical framework. Gender may, in fact, play a role in consciousness, and therefore in the recovery from general anesthesia. The covariates (total anesthetic time, body mass index, age, and total fentanyl dose) did not significantly impact recovery time. Males received significantly more propofol and fentanyl for the induction of anesthesia. We attribute this finding to the method by which anesthesia was induced, using specific amounts of each drug given per kilogram body weight. Since men weighed more they were given more drug amounts on induction of general anesthesia. This may have accounted for delays in wake-up time among males. An interesting finding however, was that BIS scores and end-tidal concentrations of

sevoflurane were similar between males and females upon recovery. The ability to generalize results from this study may be limited because the population studied may not represent the population at large. Both Gan et al. (1999) and Myles et al. (2001) studied much larger populations and at multiple sites, whereas our sample was drawn from a young, healthy population at a military installation. Additionally, neither of the investigators was blinded to any component of the study.

Conclusions

The data collected from this study are the basis for the following conclusions. First, there was no statistically significant difference in recovery from general anesthesia using sevoflurane and BIS monitoring between males and females. The covariates of total anesthetic time, body mass index, age, and total fentanyl dose did not have a significant impact on the recovery in males or females. Males received significantly higher induction doses of propofol, fentanyl and succinylcholine but had similar emergence end tidal sevoflurane and BIS monitor readings when compared to females. The subject's weight and the method by which general anesthesia was induced may account for these differences. While the average actual difference in the time it took to recover was numerically shorter for females, there was no clinical significance. A difference of 25 seconds is not clinically relevant to reducing recovery times and increasing patient satisfaction.

Implications for Nursing

Evidence from previous research suggests that gender differences exist in the recovery from general anesthesia (Gan et al. 1999 & Myles et al. 2001). As previously stated, research has demonstrated the existence of distinct sexual dimorphisms in anatomy, physiology, and pharmacology. More research is needed to substantiate the theory behind gender differences in consciousness, the implications for anesthesia, and

the application to recovery from anesthesia.

Recommendations for Further Research

We would recommend another study similar in design but with a larger sample size, one that would incorporate more clinical sites over a longer period of time. This may help elucidate whether or not a gender related difference in recovery from general anesthesia exists. Furthermore, more attempts to control the variability of adjunctive medications between genders might yield more significant results.

APPENDIX A

Data Collection Worksheet

Data Collection Worksheet

DATA COLLECTION TOOL Gender Differences in Recovery Times –Sevoflurane Study				
Demographic data:				
Random number assignment:				
Age:	Height: in.	Weight: kg	BMI: kg/m^2	Sex: M F
ASA Classification: I II		Surgical Procedure:		
Preoperative Information:				
Medical History:				
Current Medications:				
Baseline BIS Value:		Midazolam: mg total/ mg/kg dose		
Adjuctive medication and doses:				
Intraoperative Information:				
Propofol induction dose: Range (1.5-2 mg/kg) mg given		Fentanyl total induction dose: Dose (2 mcg/kg) mcg given (A)		Fentanyl supplemental doses: (50-100 mcg increments) mcg supp'd (B) mcg total (A+B)
Vecuronium total dose: (0.1 mg/kg) mg given		RSI: yes no Succinylcholine Dose (1.0 mg/kg)		Total dose:
Average end-tidal sevoflurane concentration (%):				
Average BIS Value (Intraoperative):				
Adjunctive medication and doses:				
Outcome Criteria Data:				
Time zero: sevoflurane off			BIS value:	End tidal sevoflurane concentration (%):
Time to opening of eyes: min. secs.			BIS value:	End tidal sevoflurane concentration (%):
Time to hand grip & release: min. secs.			BIS value:	End tidal sevoflurane concentration (%):
Elapsed time to achieve both recovery criteria: min. secs.				
Total Anesthetic Duration: hrs. min.				
Investigator:			Data collector:	

Intraoperative Readings

1st Hr	00	05	10	15	20	25	30	35	40	45	50	55
BIS value (0-100)												
E/T (%) Sevoflurane												

2nd Hr	00	05	10	15	20	25	30	35	40	45	50	55
BIS value (0-100)												
E/T (%) Sevoflurane												

3rd Hr	00	05	10	15	20	25	30	35	40	45	50	55
BIS value (0-100)												
E/T (%) Sevoflurane												

Outcome Criteria - Measurement Readings

Patient Response	Time Zero	1 min	2 min	3 min	4 min	5 min	6 min	7 min	8 min	9 min	10 min
Eye Opening											
Hand Grip & Release											
BIS value (0-100)											
E/T (%) Sevoflurane											

Patient Response	11 min	12 min	13 min	14 min	15 min	16 min	17 min	18 min	19 min	20 min	21 min
Eye Opening											
Hand Grip & Release											
BIS value (0-100)											
E/T (%) Sevoflurane											

****Legand:**
BIS = Bispectral Index monitor
RSI = rapid sequence intubation
Sevo = Sevoflurane
kg/m^2 = kilogram per meter (squared)
supp'd = supplemented
secs. = seconds min. = minutes hrs. = hours
in. = inches kg = kilograms
mg = milligrams mcg = micrograms
E/T = End-tidal Concentration (% fraction) on respiratory gas monitor (RGM)
Eye opening and Handgrip Response: ✓ = stimulated with no response, ✕ = stimulated and met criteria

APPENDIX B

Sample Consent

Sample Consent

INFORMED CONSENT DOCUMENT

60TH MEDICAL GROUP
David Grant Medical Center
101 Bodin Circle
Travis AFB, CA 94535-1800

Privacy Act of 1974 and Health Insurance Portability And Accountability Act (HIPAA) applies. DD Form 2005 filed in and Notice of Privacy Practices label contained on the outside of Clinical/Medical Records.

PRIVACY ISSUES: *Protected health information (PHI) is any health information about you that can reasonably be used to identify you by the person to whom it is provided. The people who are conducting the study (the "Researchers") may need to look at your medical and study records that contain PHI. Records of your participation in this study may only be disclosed in accordance with federal law, including the Federal Privacy Act, 5 USC 552, HIPAA, and their implementing regulations. DD Form 2005 contains the Privacy Act Statement for the records. Government agencies that make rules and policies about how research is done, including the Office for Human Research Protections (OHRP) and the Food and Drug Administration (FDA), have the right to review these records, if applicable.*

TITLE OF STUDY

GENDER DIFFERENCES IN RECOVERY TIMES FROM GENERAL ANESTHESIA USING SEVOFLURANE AND BISPECTRAL INDEX MONITOR

INVESTIGATORS' NAMES, DEPARTMENTS, PHONE NUMBERS

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Keith R. Anderson, Capt, USAF, NC, B.S.N., 60th MSGS/SGCSA, 423-3590

INTRODUCTION

It is important that you read and understand several general principles that apply to all who take part in research studies: (a) taking part in the study is entirely voluntary; (b) personal benefit may not result from taking part in the study, but knowledge may be gained that will benefit others; (c) you may withdraw from the study at any time without penalty or loss of any benefits to which you are otherwise entitled. The nature of the study, the risks, inconveniences, discomforts, and other pertinent information about the study are discussed below. If you have personal, religious or ethical beliefs, which you think, might limit the types of medical treatment (for example, blood transfusions) that you would agree to receive; you should discuss them fully with your physician(s) before entering this study. You are urged to discuss any questions you have about this study with your doctor(s) and/or the clinic staff members.

PURPOSE OF STUDY

(This section will explain the nature, purpose(s), approximate number of subjects, and the duration of participants' involvement.)

You, _____ (SSN: ___ - ___ - ____), understand that you are being asked to participate in a research study. The purpose of this study is to see if there is a difference in wake up times between men and women after general anesthesia using sevoflurane, a common gas used in anesthesia. There will be 60 patients in the study: 30 males and 30 females. Your participation will start from the time you meet your anesthesia provider the day of your surgery until you are admitted to the post-operative recovery room following your surgery.

PROCEDURES

(This section will explain all procedures and the purpose of the procedures to be undergone as part of this study. Any experimental procedures will be explained as such.)

On the day of your surgery, while in the holding room, an IV will be started in one of your arms. The anesthesia provider

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and operating room nurse will greet you, check your ID band and your chart. You will then be given medications to help you relax prior to being taken to the operating room. Once in the operating room equipment will be placed to evaluate how fast your heart is beating, how well you are breathing and to check your blood pressure. In this study, a "sticky" strip will be place on your forehead to measure how "asleep" you are. A mask will be place on your face, you will be asked to place your chin up and to take deep breaths. Medications will be given through your vein catheter to make you pain free and fall asleep. You may feel "stinging" where the medication is entering your vein; this is normal and will soon go away. After you are asleep, a breathing tube will be placed into your throat for the rest of your surgery. A common anesthetic gas (sevoflurane) used for this study will then be turned on. During your surgery information will be collected every five minutes until the surgery is complete. After your surgery is complete and all bandages have been placed, the anesthetic gas will be turned off and information will be collected every minute until you can open your eyes and grab and release the anesthesia provider's hand when asked. Once you are able to complete these tasks your participation requirements for this study are complete. The remainder of your care will be routine.

BENEFITS

You understand that no benefits can be guaranteed. By participating in this study an additional monitor, the Bispectral Index Monitor, will be used. This monitor fastens to the forehead by a "sticky" strip and provides the anesthesia provider an additional means of evaluating your level of sleep. It also has the potential benefit of requiring the use of less anesthetic drugs and/or faster recovery from anesthesia.

ALTERNATIVES

(This section will explain your alternative treatment possibilities)

The alternative is for you not to participate in the study. Your care will not be influenced in any way, should you choose not to participate.

RISKS/INCONVENIENCES

(Any discomfort , risks. inconveniences caused from procedures or drugs used that may be expected from participation in this study.)

Your participation in this research study involves procedures or the use of medications that could possibly present a risk to unborn children. Since this possibility exists, your physician will do a serum (blood) or urine pregnancy test before you participate in the study. The risks associated with anesthesia were explained to you in the consent for general anesthesia. A risk associated from participating in this study includes a potential for a skin reaction to the "sticky" strip that will be attached to your forehead. This skin reaction may cause redness, itching, hives, blisters, and/or other local skin irritations. Although extremely unlikely, a more serious reaction, such as, an anaphylactic reaction to the "sticky" strip, is possible.

EVENT OF INJURY

You understand that your entitlement to medical and dental care and/or compensation in the event of injury is governed by federal laws and regulations, and if you have questions about your rights or if you believe you have received a research-related injury, you may contact the 60th Medical Group (DGMC) Patient Advocate, at (707) 423-2388, the Director of the Clinical Investigation Facility at (707) 423-7400, and/or the investigator Katherine J. Alguire, Capt, USAF, NC, NAR at (707) 423-3590, Beeper (707) 420-6440.

OCCURRENCE OF UNANTICIPATED EVENT

If an unanticipated event (clinical or medical misadventure) occurs during your participation in this study, you will be informed. If you are not competent at the time to understand the nature of the event, such information will be brought to the attention of your guardian or next of kin.

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CONFIDENTIALITY AND PROTECTED HEALTH INFORMATION (PHI)
(If Applicable- Please Complete All Blanks)
(The following statement is to be included and applies ONLY if it is known that commercial or outside use of donated samples is anticipated.)

We will not use or disclose your records in any ways other than the ways we describe in this form, and we will keep your records private to the extent allowed by law.

Under the Health Insurance Portability and Accountability Act (HIPAA), a federal law enacted to protect the privacy of your protected health information (PHI), before we can use or disclose your PHI, we must provide you with information about what PHI will be used and how it will be used and disclosed.

Your protected health information that may be used and disclosed in this study includes:
- weight, height, medical history
- surgical procedure

Your protected health information will be used for: The purpose of this study is to see if there is a difference in wake up times between men and women after general anesthesia using sevoflurane, a common gas used in anesthesia.

The disclosure of your protected health information is necessary in order to be able to conduct the research project described. Records of your participation in this study may only be disclosed in accordance with federal law, including the Federal Privacy Act, the Health Insurance Portability and Accountability Act of 1996, 5 U.S.C.552a, and its implementing regulations. DD Form 2005, Privacy Act Statement - Military Health Records, contains the Privacy Act Statement for the records. Note: Protected health information of military service members may be used or disclosed for activities deemed necessary by appropriate military command authorities to ensure the proper execution of the military mission.

By signing this authorization, you give your permission for information gained from your participation in this study to be published in medical literature, discussed for educational purposes, and used generally to further medical science. You will not be personally identified; all information will be presented as anonymous data.

If you decide to participate in this research, then you will be agreeing to let the Researchers and any other persons, companies or agencies described below use and share your PHI for the study in the ways that are set forth in this section, so please review this section very carefully.

The Principal Investigator may use and share your health information with:
- 60 MDG Institution Review Board
- Government representatives, which required by law
- DGMC or Department of Defense representatives
- University of Texas, Houston Health Science Center
- US Army Graduate Anesthesia Program
- Journal of Anesthesiology or similar publication

The researchers, representatives at the University of Texas and US Army Graduate Program agree to protect your health information by using and disclosing it only as permitted by you in this authorization and as directed by state and federal law.

If your protected health information is disclosed to anyone outside of this study, the information may no longer be protected under this authorization.

You do not have to sign this authorization. If you decide not to sign the Authorization, it will not affect your treatment.

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payment or enrollment in any health plans or affect your eligibility for benefits. By not signing, you may not be allowed to participate in the research study.

If you decide you want to revoke your authorization for us to use your PHI, you may do so by completing, signing a revocation letter and forwarding the letter to the PI. O

Your Right Under HIPAA to Revoke Your Authorization: Giving the Researchers your authorization to use and share your PHI is voluntary. At any time, you may choose to revoke your authorization for the Researchers to use and share your PHI. If you revoke your authorization, the Researchers may no longer be able to provide you with any research-related treatment, but your revocation will not otherwise affect your current or future health care. Further, if you revoke your authorization, there will be no penalty or loss of any benefits to which you are otherwise entitled.

If you decide you want to revoke your PHI authorization, prepare and sign a revocation letter. Forward the letter to the PI. Once we receive your written revocation of your authorization to use your PHI, we will not make any other use of your PHI or share it with anyone else, except as follows:

(a) we will let any other previously identified parties know that you have revoked your authorization;

(b) we will not ask any identified parties to return any data that we provided to it/them before you revoked your authorization;

(c) and, even after we receive your revocation, we will still provide them and any other parties to whom we stated that we would disclose data with any data that is necessary to preserve the integrity of the research study, and we will provide any governmental or other MDG/CC approved agency with any data that they may need in order to comply with/or investigate adverse events or non-compliance with any applicable laws or instructions.

PHI May be Re-disclosed: If we disclose your PHI to one of the other parties described above, that party might further disclose your PHI to another party. After the study is concluded and the data has been transmitted to the national agency sponsoring the study, the responsibility of DGMC is ended.

Expiration Date or Event: End of the study and any applicable records retention period.

DECISION TO PARTICIPATE

The decision to participate in this study is completely voluntary on your part. No one has coerced or intimidated you into participating in this program. You are participating because you want to. Your investigator(s) has adequately answered any and all questions you have about this study, your participation, and the procedures involved. You understand that the investigator will be available to answer any questions concerning procedures throughout this study. You understand that if significant new findings develop during the course of this study that may relate to your decision to continue participation, you will be informed. You further understand that you may withdraw this consent at any time and discontinue further participation in this study without prejudice to your entitlement to care. You also understand that the investigator of this study may terminate your participation in this study at any time if you feel this to be in your best interest. You have been provided a copy of this consent form.

(Volunteer's Initials)

Your signature below indicates your willingness to participate in this research study and serves as your consent to release your protected health information.

(Subject's Printed Name)	(Subject's SSN)	
(Subject's Signature)	(FMP* & Sponsor's SSN)	(Date)
(Advising Investigator's Signature)	(Investigator's SSN)	(Date)
(Witness's Signature)	(Witness's SSN)	(Date)

Distribution:
(1) Clinical Investigation Facility (60MDSS/SGSE), [original]
(2) Research Volunteer;
(3) Volunteer's Outpatient Medical Record, (permanently maintained);
(4) Principal Investigator.

* FMP (Family Member Prefix) such as 20 - sponsor, 30 - dependent spouse, 01 - first child, etc...)

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(Volunteer's Initials)

REFERENCES

Abernathy, D., Divoll, M., Greenblatt, D., & Ameer, B. (1982). Obesity, sex, and acetaminophen disposition. Journal of Clinical and Therapeutic Pharmacology, 31(6), 783-790.

Alifimoff, K., & Miller, J. (1998). Mechanism of action of general anesthetics. In Longnecker, D., Tinker, J., Morgan, G. (Ed.), Principles and practice of anesthesiology (2nd ed., pp. 1103-1121). St. Louis: Mosby.

Aspect Medical systems (2000). BIS Monitor. (Retrieved 9 December 2001). From the World Wide Web: http://www.aspectms.com/products/products_index.htm.

Badrinath, S., Avramov, M., Papaioannou, M., & Ivankovich, A. (1999). The impact of EEG-bispectral index monitoring on drug usage and recovery during ambulatory anesthesia. Anesthesia and Analgesia, 88, 518.

Bard, J., (2001). The BIS monitor: a review and technology assessment. AANA Journal, 69, 477-483.

Bartok, R., & Craft, R. (1997). Sex differences in opioid antinociception. The Journal of Pharmacology and Experimental Therapeutics, 282, 769-778.

Benet, L.Z. (1996). General Principles: Introduction. In Hardman, J. & Limbird, L. (Eds.), Goodman & Gilman's the pharmacological basis of therapeutics (9th ed., p. 3). New York: McGraw-Hill.

Chen, M., Lee, S., Ng, M., Schuirmann, D., Lesko, L., & Williams, R. (2000). Pharmacokinetic analysis of bioequivalence trials. Clinical Pharmacology and Therapeutics, 68, 510-521.

Correia, M. (2001). Drug Biotransformation. In Katzung, B. (Ed.), Basic and clinical pharmacology (8th ed., pp. 60). New York: Lange Medical Books/ McGraw-Hill.

Degoute, C., Macabeo, C., Dubreuil, C., Duclaux, R., & Banssillon, V. (2001). EEG bispectral index and hypnotic component of anaesthesia induced by sevoflurane: comparison between children and adults. British Journal of Anaesthesia, 86, 209-212.

Domino, K., Posner, K., Caplan, R., & Cheney, F. (1999). Awareness during anesthesia: a closed claims analysis. Anesthesiology, 90, 1053-1061.

Ebert, T., Robinson, B., Uhrich, T., Mackenthun, A., & Pichotta, P. (1998). Recovery from sevoflurane anesthesia: a comparison to isoflurane and propofol anesthesia. Anesthesiology, 89, 1524-1531.

Fang, Z., Kandel, L., Laster, M., Ionescu, P., & Eger II, E. (1996). Factors affecting production of compound A from the interaction of sevoflurane with baralyme and soda lime. Anesthesia and Analgesia, 82, 775-781.

Fredman, B., Nathanson, M., Smith, I., Wang, J., Klein, K., & White, P. (1995). Sevoflurane for outpatient anesthesia: A comparison with propofol. Anesthesia and Analgesia 81, 823-828.

Frink, E., Malan, P., Atlas, M., Dominguez, L., DiNardo, J., & Brown, B. (1992). Clinical comparison of sevoflurane and isoflurane in healthy patients. Anesthesia and Analgesia 74, 241-245.

Gan, T., Glass, P., Windsor, A., Payne, F., Rosow, C., Sebel, P., & Manberg, P. (1997). Bispectral index monitoring allows faster emergence and improved recovery from propofol, alfentanil, and nitrous oxide anesthesia. Anesthesiology, 87, 808-815.

Gan, T., Glass, P., Sigl, J., Sebel, P., Payne, F., Rosow, C., & Embree, P. (1999). Women emerge from general anesthesia with propofol/alfentanil/nitrous oxide faster than men. Anesthesiology, 90, 1283-1287.

Gear, R., Miaskowski, C., Gordon, N., Paul, S., Heller, P., & Levine, J. (1996). Kappa-opioids produce significantly greater analgesia in women than in men. Nature Medicine, 2, 1248-1250.

Gear, R., Miaskowski, C., Gordon, N., Paul, S., Heller, P., & Levine, J. (2000). Action of naloxone on gender-dependent analgesic and antianalgesic effects of nalbuphine in humans. Journal of Pain, 1(2), 122-127.

Gennaro, A., Nora, A., Nora, J., Stander, R., Weiss, L., & Igoe, J. (Eds.). (1979). Blakiston's pocket medical dictionary (4th ed.). New York: McGraw-Hill Book Company.

Gerdin, E., & Rane, A. (1992). N-demethylation of ethlymorphine in pregnant and non-pregnant women and in men: an evaluation of the effects of sex steroids. British Journal of Clinical Pharmacology, 34, 250-255.

Ghoneim, M., & Block, R. (1997). Learning and memory during general anesthesia: an update. Anesthesiology, 87, 387-410.

Glass, P., Bloom, M., Kearse, L., Rosow, C., Sebel, P., & Manberg, P. (1997). Bispectral analysis measures sedation and memory effects of propofol, midazolam, isoflurane, and alfentanil in healthy volunteers. Anesthesiology, 86, 836-847.

Greenblatt, D., Abernathy, D., Locnisar, A., Harmatz, J., Limjuco, R., & Shader, R. (1984). Effect of age, gender, and obesity on midazolam kinetics. Anesthesiology, 61, 27-35.

Greenblatt, D., Divoll, M., Harmatz, J., & Shader, R. (1980). Oxazepam kinetics: effects of age and sex. The Journal of Pharmacology and Experimental Therapeutics, 215(1), 86-91.

Halliburton, J.R., (1998). Awareness during general anesthesia: new technology for an old problem. CRNA: The Clinical Forum for the Nurse Anesthetist, 9,39-43.

Hobson, J. (1997). Counsciousness: lessons for anesthesia from sleep resrch. In aksh, T (Ed.), Anesthesia: biologic foundations (1 ed., pp. 423-425). Philadelphia: Lippincott-Raven.

Holaday, D., & Smith, F. (1981). Clinical Characteristics and biotransformation of sevoflurane in healthy human volunteers. Anesthesiology, 54, 100-106.

Hooper, W., & Qing, M. (1990). The influence of age and gender on the stereoselective metabolism and pharmacokinetics of mephobarbital in humans. Clinical Pharmacological Therapy, 48, 633-640.

Hunt, C., Westerkam, W., & Stave, G. (1992). Effect of age and gender on the activity of human hepatic CYP3A. Biochemical Pharmacology, 44(2), 275-283.

Ibrahim, A., Ghoneim, M., Kharasch, E., Epstein, R., Groudine, S., Ebert, T., Binstock, W., & Philip, B. (2001). Speed of recovery and side effect profile of sevoflurane sedation compared with midazolam. Anesthesiology, 94, 87-94.

Jellish, W., Lien, C., Fontenot, H., & Hall, R. (1996). The comparative effects of sevoflurane versus propofol in the induction and maintenance of anesthesia in adult patients. Anesthesia and Analgesia, 82, 479-485.

Johansen, J., & Sebel, P. (2000). Development and clinical application of electroencephalographic bispectrum monitoring. Anesthesiology, 93, 1336-1344.

Kando, J., Yonkers, K., & Cole, J. (1995). Gender as a risk factor for adverse events to medications. Drugs, 50(1), 1-6.

Kato, R., & Yamazoe, Y. (1992). Sex-specific cytochrome P450 as a cause of sex and species-related differences in drug toxicity. Toxicology Letters, 64/65, 661-667.

Katoh, T., Suzuki, A., & Ikeda, K. (1998). Electroencephalographic derivatives as a tool for predicting the depth of sedation and anesthesia induced by sevoflurane. Anesthesiology, 88, 642-650.

Kavaliers, M., Colwell, D., & Choleris, E. (1998). Sex differences in opioid and N-methyl-D-aspartate mediated non-opioid biting fly exposure induced analgesia in deer mice. Pain, 77, 163-171.

Kepler, K., Standifer, K., Paul, D., Kest, B., Pasternak, G., & Bodnar, R. (1991). Gender effects of central opioid analgesia. Pain, 45, 87-94.

Kharasch, E., & Jubert, C. (1999). Compound A uptake and metabolism to Mercapturic acids and 3,3,3-trifluoro-2-fluoromethoxypropanoic acid during low –flow sevoflurane anesthesia: biomarkers for exposure, risk assessment, and interspecies comparison. Anesthesiology 91, 1267.

Lasaga, M., Duvilanski, B., Seilicovich, A., Afione, S., & Debeljuk, L. (1988). Effects of sex steroids on GABA receptors in the rat hypothalamus and anterior pituitary gland. European Journal of Pharmacology, 155, 163-166.

Liu, J., Singh, H., & White, P. (1997). Electroencephalographic bispectral index correlates with intraoperative recall and depth of propofol-induced sedation. Anesthesia and Analgesia, 84, 185-189.

Longnecker, D., Tinker, J., & Morgan, E. (Eds.). (1998). Principles and practice of anesthesiology (2nd ed.). St. Louis: Mosby.

Maggi, A., & Perez, J. (1984). Progesterone and estrogens in rat brain: modulation of GABA (gamma aminobutyric acid) receptor activity. European Journal of Pharmacology, 103, 165-168.

Merkatz, R., Temple, R., Sobel, S., Feiden, K., & Kessler, D. (1993). Women in clinical trials of new drugs - a change in Food and Drug Administration policy. The New England Journal of Medicine, 329, 292-296.

Miller, K., & Alifimoff, J. (1998). Mechanism of action of general anesthetic agents. In Longnecker, D., Tinker J., & Morgan, G. (Eds.), Principles and practice of anesthesiology (2nd ed., pp. 1103-1119). St. Louis: Mosby.

Mogil, J., Richards, S., O'Toole, L., Helms, M., Mitchell, S., Kest, B., & Belknap, J. (1997). Identification of a sex-specific quantitative trait locus mediating nonopioid stress induced analgesia in female mice. The Journal of Neuroscience, 17(20), 7995-8002.

Myles, P., McLeod, A., Hunt, J., & Fletcher, H. (2001). Sex differences in speed of emergence and quality of recovery after anaesthesia: cohort study. British Medical Journal, 322(7288), 710-711.

Nathanson, M., Fredman, B., Smith, I., & White, P. (1995). Sevoflurane versus desflurane for outpatient anesthesia: a comparison of maintenance and recovery profiles. Anesthesia and Analgesia, 81, 1186-1190.

Nelskyla, K., Yli-Hankala, A., Puro, J., & Korttila, K. (2001). Sevoflurane titration using bispectral index decreases postoperative vomiting in phase II recovery after ambulatory surgery. Anesthesia and Analgesia, 93, 1165-1169.

Ochs, H., Greenblatt, D., Divoll, M., Abernathy, D., Feyerabend, H., & Dengler, H. (1981). Diazepam kinetics in relation to age and sex. Pharmacology, 23, 24-30.

Olofsen, E., & Dahan, A. (1999). The dynamic relationship between end-tidal sevoflurane and isoflurane concentrations and bispectral index and spectral edge frequency of the electroencephalogram. Anesthesiology, 90, 1345-1353.

Ouellette, S., & Simpson, C. (1998). Monitoring for intraoperative awareness. AORN Journal, 68, 950, 952-953, 955-95, 959-961.

Peduto, V., Mezzetti, D., Properzi, M., & Giorgini, C. (2000). Sevoflurane provides better recovery than propofol plus fentanyl in anaesthesia for day-care surgery. European Journal of Anaesthesiology, 17, 136-143.

Philip, B., Kallar, S., Bogetz, M., Scheeler, M., & Wetcher, B. (1996). A multicenter comparision of maintenance and recovery with sevoflurane or isoflurane for adult ambulatory anesthesia. Anesthesia and Analgesia, 83,314-319.

Ross, E. (1996). Pharmacodynamics. In Hardman, J., Limbird, L. (Ed.), Goodman & Gilman's the pharmacological basis of therapeutics (9th ed., p. 29). New York: McGraw-Hill.

Routledge, P., Stargel, W., Kitchell, B., Barchowsky, A., & Shand, D. (1981). Sex-related differences in the plasma protein binding of lignocaine and diazepam. British Journal of Clinical Pharmacology, 11, 245-250.

Schnider, R., Luginbuhl, M., Peterson-Felix, S., & Mathis, J. (1997). Unreasonably low bispectral index values in a volunteer with genetically determined low voltage electroencephalographic signal. Anesthesiology, 87, A502.

Sebel, P., Lang, E., Rampil, I., White, P., Cork, R., Jopling, M., Smith, N., Glass, A., & Manberg, P. (1997). A multicenter study of bispectral electroencephalogram analysis for monitoring anesthetic effect. Anesthesia and Analgesia, 84, 891-899.

Shiraishi, Y., & Ikeda, K. (1990) Uptake and biotransformation of sevoflurane in humans: a comparative study of sevoflurane with halothane, enflurane, and isoflurane. Journal of Clinical Anesthesia, 2, 381-386.

Skett, P. (1988). Biochemical basis of sex differences in drug metabolism. Therapeutic Pharmacology, 38, 269-304.

Smith, I., Ding, Y., & White, P. (1992). Comparison of induction , maintenance, and recovery characteristics of sevoflurane-N_20 and propofol-sevoflurance-N_20 with propofol-isoflurance-N_20. Anesthesia and Analgesia, 74, 253-259.

Smith, I., Nathanson, M., & White, P. (1995). The role of sevoflurane in outpatient anesthesia. Anesthesia and Analgesia, 81, 67S-2S.

Song, D., Joshi, G., & White, P. (1997). Titration of volatile anesthetics using bispectral index facilitates recovery after ambulatory anesthesia. Anesthesiology, 87 842-848.

Song, D., Joshi, G., & White, P. (1998). Fast-track eligibility after ambulatory anesthesia: a comparison of desflurane, sevoflurane, and propofol. Anesthesia and Analgesia, 86, 267-273.

Strum, E., & Eger, E. (1987). Partition coefficients for sevoflurane in human blood, saline, and olive oil. Anesthesia and Analgesia, 66, 654-656.

Taber, C. (1985). "Counsciousness". In Davis, F. (Ed.), Taber's cyclopedic medical dictionary (15th ed., p. 373). Philadelphia: F.A. Davis.

Walker, J., & Carmody, J. (1998). Experimental pain in healthy human subjects: gender differences in nociception and in response to ibuprofen. Anesthesia and Analgesia, 86, 1257-1262.

Yasuda, N., Lockhart, S., Eger, E., Weiskopf, R., Liu, J., Laster, M., Taheri, S., & Peterson, N. (1991). Comparison of kinetics of sevoflurane and isoflurane in humans. Anesthesia and Analgesia, 72. 316-324.

Yovel, G., Shakhar, K., & Ben-Eliyahu, S. (2001). The effects of sex, menstrual cycle, and oral contraceptives on the number and activity of natural killer cells. Gynecologic Oncology, 81, 254-262.

VITAE

Katherine J. Alguire was born in Lincoln, Nebraska on [redacted], [redacted], the daughter of [redacted] and [redacted]. She earned her GED from the state of Kansas in 1985. In 1992 she graduated with the degree of an Associate of Science in Nursing from Johnson County Community College in Overland Park, Kansas. She received the degree of a Bachelor of Science in Nursing from Webster University in 1996. From 1992 to 1998 she was employed as a nurse at hospitals in the greater Kansas City area. Since 1998 she has been an officer on active duty in the United States Air Force, Nurse Corps. She has been married to Guerdon Moulton Alguire since 1985. They have three children, Sarah Anne, Steven James and Samantha Elizabeth.

VITAE

Keith R. Anderson was born in Alameda, California on [redacted], the son of [redacted]. and [redacted]. In June of 1984, he earned a diploma from Jefferson High School in Jefferson, Oregon. He then received a Bachelor's of Science in Nursing from the Oregon Institute of Technology in June of 1989. From 1989 to 1995 he worked at Salem Hospital in Salem Oregon. Since 1996, he has served on active duty in the United States Air Force, as a commissioned officer in the Nurse Corps. He has been married to Sonja Ingrid Anderson since 1989. They have three children, Caarin Elizabeth, Graeme Michael, and Reid Spencer.